

REMARKS

Applicants acknowledge with appreciation the reclassification of Claim 5 as being within the elected group.

Claim Amendments

Claims 21, 36 and 78 have been canceled without prejudice and without disclaimer of the subject matter.

Applicants have amended claim 56 as helpfully suggested by the Examiner.

Applicants have amended claims 1, 34, and 47 to recite elected subject matter and by specifying that the dominant negative allele of the mismatch repair gene is a mammalian *PMS2* gene. Dependent claims 21, 36 and 78 have been canceled as redundant. Claims 5, 20, and 35 have been amended to recite that the dominant negative mismatch repair gene is a human *PMS2*.

Applicants have amended claims 17, 33, and 85 to clarify that the nucleotide change at nucleotide 424 is for the human PMS2 truncation mutant.

Applicants have amended claim 18 to specify that the plant cell is of a plant seedling. Support for this amendment may be found, for example, at page 10, lines 10-11 which teaches, “According to one process of producing a transgenic plant, the polynucleotide is transfected into the plant seedling.” Claim 19 has been amended to clarify that the plant seedling is grown into a mature plant.

35 U.S.C. §112, first paragraph

(a) Enablement

Claims 1, 2, 5, 15-21, 31-36, 47, 77-79, and 83-85 stand rejected as the specification allegedly does not provide sufficient enablement for use of genes other than human PMS2-134. The specification, therefore, is allegedly not commensurate with the scope of the claims. Claims 21, 36, and 78 have been canceled. Thus the rejection of these claims is rendered moot. Applicants respectfully traverse the rejection as it applies to claims 1, 2, 5, 15-20, 31-35, 47, 77, 79, and 83-85.

Claims 1, 2, 5, 15-20, and 31-33 are directed to a method for making a hypermutable cell comprising introducing into a plant cell a polynucleotide comprising a dominant negative allele of a mammalian PMS2 gene. Claims 34 and 35 are directed to a homogeneous composition of cultured, hypermutable, plant cells which comprise a dominant negative allele of a mammalian PMS2 mismatch repair gene. Claims 47, 77, 79, and 83-85 are directed to a hypermutable transgenic plant wherein at least 50% of the cells of the plant comprise a dominant negative allele of a mammalian PMS2 mismatch repair gene.

To satisfy the enablement requirement, the specification of a patent must teach those skilled in the art how to make and use the full scope of the claimed invention without undue experimentation. *In re Wright*, 999 F.2d 1557 (Fed. Cir. 1993). The specification meets this requirement.

The Office Action alleges that the specification does not provide sufficient guidance for making and using any mammalian *PMS2* gene or making and using truncation mutations in any mammalian *PMS2* gene. (Paper 16, page 8, lines 4-7.) The specification, however, discloses a sufficient number of *PMS* genes containing dominant negative mutations for one

of skill in the art to make and use the claimed invention without resorting to undue experimentation. The specification discloses the nucleotide and amino acid sequence of the human and plant *Arabidopsis thaliana* *PMS2* genes and the nucleotide and amino acid sequence of human and *A. thaliana* *PMS2* genes encoding a truncation mutation. Despite their evolutionary distance, these genes are closely related. The specification discloses that the human and *A. thaliana* *PMS134* genes share 53.2% nucleotide sequence identity and 65.1% and 50.7% amino acid sequence similarity and identity, respectively. (See Figures 6 and 7, respectively). The specification also discloses the close evolutionary homology of human and plant *PMS2* in a cladogram (Figure 5).

Expression of the truncated human and plant *A. thaliana* *PMS2* genes in cells induces the same phenotype. “The results from these studies show that cells expressing the hPMS134 or the ATPMS134 polypeptides displayed increased mutation rates in the genome of the DH10B bacterial strain which resulted in the production of KAN resistant clones (Figure 9).” (Page 17, lines 3-6.) Thus, the specification provides *working examples* of human and plant truncation mutants of *PMS2* each of which exerts a dominant negative effect.

Given the level of structural and functional relatedness of the human and plant *PMS2* genes one of skill in the art would expect any mammalian *PMS2* gene to function similarly. Indeed, this is the case. The mouse *PMS2* gene was cloned and sequenced prior to the effective filing date of the application, February 18, 2000. The nucleic acid and amino acid sequences of the mouse *PMS2* gene were published under GenBank Accession Number U28724.1 on February 9, 1996. (Exhibit A.) The amino acid sequence of the mouse *PMS2* gene shares 73% amino acid sequence identity and 80% amino acid sequence homology with

the human *PMS2* gene shown in SEQ ID NO:11. (Exhibit B.) Thus one of skill in the art, using the specification's disclosures regarding the human and plant *PMS2* genes and the known sequence of the mouse *PMS2* gene would have been able to make and use any mammalian *PMS2* gene as recited in the rejected claims. Because the truncation of the human and plant *PMS2* genes produces a dominant negative phenotype in cells, one of skill in the art would also have expected similar truncation mutations in other mammalian *PMS2* genes to have a similar effect.

The specification also provides one of skill in the art with guidance to aid in the selection of other dominant negative mutations that can be used in the claimed methods, cells or plants. The specification teaches one of skill in the art a proposed mechanism of action of the dominant negative effect. The specification discloses that a dominant negative *PMS2* gene may be a "mutation which leads to a protein product which is able to complex with other members of the MMR complex but which is not functional." (Page 7, lines 25-28.) The specification also teaches one of skill in the art how to test if a mutated *PMS2* allele contains a dominant negative mutation. (See page 7, lines 28-29; page 21, lines 13-24; and page 21, line 28 to page 22, line 3.) Thus, the specification provides sufficient disclosure of species of *PMS2* alleles, in conjunction with a structure/function relationship of the genes that exert a dominant-negative effect, to enable one of skill in the art to make and use the claimed mammalian *PMS2* mismatch repair genes.

The Office Action cites two references in support of its assertion that the rejected claims are not enabled. Chang (*Genome Research* (2001) 1:1145-1146) is cited for teaching that mutation of minor proteins involved in mismatch repair (MMR), such as PMS2, may not result in loss of cellular MMR function and that if MMR function is lost in the cell it is slight

because other proteins in the cell can compensate for the loss of the minor protein. (Paper 16, page 9, lines 2-5.) Pang (*Mol. and Cell. Biol.* (1997) 17:4465-4473) is cited for teaching that yeast *PMS1p*, a yeast homolog of the mammalian *PMS2* gene, does not have a dominant effect when expressed in yeast cells. (Paper 16, page 9, lines 6-9.) The Office Action concludes that the art teaches that it is unpredictable whether a mutation in the *PMS2* gene, which encodes a minor MMR protein, will impair MMR function in a cell. Thus the Office Action asserts that it would have required undue experimentation for one of skill in the art to screen a myriad of mammalian *PMS2* mutated alleles to identify those that could be used in the instant method. (Paper 16, page 9, lines 10-16.)

First, Chang merely *speculates* that a mutation in *PMS2* may not result in loss of cellular MMR function or that if any loss is detected it is slight. Chang teaches:

However, when one of the minor proteins is impaired, MMR function is retained or only partially perturbed because MSH3 and MSH6 have some functional redundancy and can compensate, at least in part, for the loss of the missing proteins. The case **may** be similar with PMS2 (PMS1 in yeast) and MLH3.

Page 1146, column 1, lines 8-15, emphasis added. Thus, Chang does not teach that loss of *PMS2* function in a cell *will* result in no or only slight loss of MMR function. Chang provides no data regarding *PMS2*. In any event, the specification discloses that dominant negative mutations in *PMS2* in fact do result in loss of mismatch repair function. Thus, *PMS2* function is not compensated by another protein in cells that express dominant negative *PMS2*. Second, it is true that Pang teaches a single truncated *PMS2* protein, *Pms1p(1-271)*, does not cause a dominant negative phenotype in yeast. Pang also teaches, however, several other *PMS2* proteins that exert a dominant negative phenotype in yeast, *Pms1p(692-904)* and *Pms1p-F126A*. See Table 1 on page 4470. Pang further teaches portions of the *PMS2*

protein that can be deleted to produce organisms that are deficient in DNA mismatch repair (DMR).

Our results indicate that the carboxyl-terminal 33% of Mlh1p (not including the last 13 amino acids) and the carboxyl-terminal 23% of Pms1p are sufficient for Mlh1p-Pms1p interaction. Deletion of the interaction domains resulted in loss of both DMR function and Mlh1p-Pms1p interaction. However, deletion constructions containing only the Pms1p-interactive domain [Mlh1p(501-769)] or the Mlh1p-interactive domain [Pms1p(692-904)] retained Mlh1p-Pms1p dimerization activity but abolished DMR function.

Page 4471, column 1, lines 22-31. Thus, while Pang teaches one truncated PMS2 protein whose expression does not result in a dominant negative mismatch repair phenotype in yeast, Pang also teaches several truncated PMS2 proteins and one mutated PMS2 protein whose expression does result in a dominant negative mismatch repair phenotype in yeast. Pang also provides guidance on which portions should be deleted to produce a dominant negative effect. See quotation above. Thus while it is not 100% predictable that a mutation in a PMS2 protein will result in a dominant negative mismatch repair phenotype, Pang demonstrates that it would not require undue experimentation to identify PMS2 mutations that confer a dominant negative mutation in a cell.

In any event, claims 17, 32, 33, and 85 should not be subject to this rejection. Each of these claims recites that the mammalian *PMS2* mismatch repair gene is a human *PMS2* mismatch repair gene and that the dominant allele comprises a truncation mutation at codon 134 or a thymidine at nucleotide 424 of wild type human *PMS2* mismatch repair gene. The Office Action acknowledges that this subject matter is enabled. The Office Action states that the specification is “enabling for a method of making a hypermutable plant cell comprising transforming said plant cell with a polynucleotide comprising nucleotide sequence that

encodes the human PMS2 134 truncation and plant cells and plants produced by said method.” (Paper 16, page 7, lines 6-9.)

Applicants respectfully submit that the claims 1, 2, 5, 15-20, 31-35, 47, 77, 79, and 83-85 are fully enabled. Withdrawal of this rejection is respectfully requested.

(b) Written Description

The Office Action rejects claims 1, 2, 5, 15-21, 31-36, 47, 77, 78, and 83-85 under 35 U.S.C. §112, first paragraph, as allegedly lacking an adequate written description. Claims 21, 36, and 78 have been canceled. Thus the rejection of these claims has been rendered moot. Applicants respectfully traverse the rejection as it applies to claims 1, 2, 5, 15-20, 31-35, 47, 77, 79, and 83-85.

In a recent Federal Circuit decision, *Moba, B.V., Staalkat, B.V., and FPS Food Processing Systems, Inc. v. Diamond Automation, Inc.* 2003 U.S. App. LEXIS 6285 (Fed. Cir. 2003), the Federal Circuit discussed the written description requirement at length. The Federal Circuit explained that its own case law shows two primary goals in the written description requirement. The first is embodied in its decision in *In re Wertheim* 541 F.2d 257, 191 USPQ 90 (CCPA 1976), and the second is embodied in its decision *Regents of the University of California v. Eli Lilly & Co.*, 119 F.3d 1559, 43 USPQ2d 1398 (Fed. Cir. 1997). The *Wertheim* court noted that “the function of the description requirement is to ensure that the inventor had possession, as of the filing date of the application relied on, of the specific subject matter *later* claimed by him.” *Wertheim* at 541 F.2d 257, 262, 191 USPQ 90, 96. As restated more recently by the Federal Circuit:

The purpose of the written description requirement is to prevent an applicant from *later* claiming that he invented that

which he did not; the applicant for a patent is therefore required “to recount his invention in such detail that his *future claims can be determined to be encompassed within his original creation.*”

Amgen Inc. v. Hoechst Merion Roussel Inc., 314 F.3d 1313, 1330, 65 USPQ2d 1385, 1397 (Fed. Cir. 2003) (citing *Vas-Cath Inc. v. Mahurkar*, 935 F.2d 1555, 1561, 19 USPQ2d 1111, 1115 (Fed. Cir. 1991) (emphasis added)).

The second goal of the written description requirement, was addressed in *Regents of the University of California v. Eli Lilly & Co.* The *Eli Lilly* court applied the written description requirement to adequacy of a description of a DNA sequence. The court held that a precise definition of the DNA sequence was required to satisfy the written description requirement, even in the absence of priority issues. The court has further refined this rule in such cases as *Enzo Biochem, Inc. v. Gen-Probe, Inc.*, 296 F.3d 1316, 63 USPQ2d 1069 (Fed. Cir. 2002) and *Amgen Inc. v. Hoechst Merion Roussel Inc.*, 314 F.3d 1313, 65 USPQ2d 1385 (Fed. Cir. 2003). In *Amgen*, the Federal Circuit clarified its holding in *Eli Lilly*, stating: “*Eli Lilly* did not hold that all functional descriptions of genetic material necessarily fail as a matter of law to meet the written description requirement; rather, the requirement may be satisfied if in the knowledge of the art the disclosed function is sufficiently correlated to a particular known structure.” *Amgen Inc. v. Hoechst Merion Roussel Inc.*, 314 F.3d at 1332. Moreover, a representative number of species within a claimed genus may fulfill the written description requirement. *The Regents of the University of California v. Eli Lilly and Company* 119 F.3d 1559, 1568 (Fed. Cir. 1997).

As discussed above, the nucleic acid and amino acid sequence of the human, mouse, and *A. thaliana* *PMS2* gene were disclosed in the specification or were known in the art prior to the effective filing date of the application. The sequences of the *PMS2* gene in human and

mouse are closely related and are representative of the recited genus of mammalian *PMS2* genes.

The specification also discloses that a truncation mutation in either of the human or *A. thaliana* *PMS2* genes results in a dominant negative *PMS2* protein. The dominant negative effect of this mutation in the *PMS2* gene of human and *A. thaliana* genes is very likely representative of the mutation in other mammalian *PMS2* alleles, thereby correlating function (dominant negative effect) with a known particular structure (truncated homologous *PMS2* sequences).

Finally, the specification provides guidance for determining the mutations in the *PMS2* gene that result in dominant negative *PMS2* proteins and how to determine if a mutation in the *PMS2* gene causes the production of a dominant negative *PMS2* protein. These disclosures in the specification demonstrate to one of skill in the art that applicants had adequately described other mutations in mammalian *PMS2* alleles.

The rejection should not apply to claims 17, 32, 33, and 85. Each of these claims recites that the mammalian *PMS2* mismatch repair gene is a human *PMS2* mismatch repair gene and that the dominant allele comprises a truncation mutation at codon 134 or that the truncation is due to a thymidine at nucleotide 424 of human *PMS2* mismatch repair gene. The Office Action acknowledges that this subject matter is described. “Applicant describes a method of making a hypermutable plant cell by transforming said plant cell with a gene encoding a truncated human *PMS2* protein, said human *PMS2* gene having been truncation mutation at codon 134 corresponding to a thymidine at position 424 of the wild-type human *PMS2* gene.” (Paper 16, page 6, lines 4-7.)

Withdrawal of this rejection to claims 1, 2, 5, 15-20, 31-35, 47, 77, 79, and 83-85 is respectfully requested.

35 U.S.C. §102(a)

The Office Action rejects claims 1, 2, 18, 19, 34, 47 and 77 under 35 U.S.C. §102(a) over PCT Publication No. WO 99/19492 to Doutriaux *et al.* (“Doutriaux”), alleging that Doutriaux teaches all the limitations of the claims through overexpression of wild-type plant mismatch repair genes.

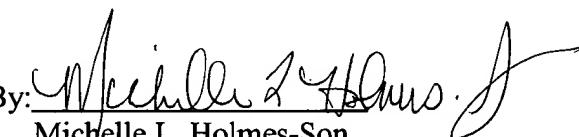
Anticipation under 35 U.S.C. §102 requires that a single prior art reference disclose each and every limitation of the claimed invention. *Electro Med. Sys. S.A. v. Cooper Life Sci.*, 34 F.3d 1048, 1052, 32 USPQ2d 1017, 1019 (Fed. Cir. 1994).

The instant claims specifically include the feature that a *dominant negative allele* of a mismatch repair gene is introduced into cells. A dominant negative allele is one that is both negative, (*i.e.*, mutant) and dominant, (*i.e.*, exerts its effect even in the presence of a wild type allele). Doutriaux neither teaches nor suggests the introduction of a *dominant negative allele*. Notably, in the passage cited by the Examiner, Doutriaux teaches that the inhibition of mismatch repair may be achieved by overexpression of the *wild-type allele* of MSH3 or MSH6, or by introduction of sense, antisense, or ribozyme sequences inhibiting mismatch repair genes, or by introducing proteins that interfere with mismatch repair (page 9, second paragraph). Nowhere does Doutriaux suggest dominant negative (*i.e.*, mutant) alleles of mismatch repair genes.

As Doutriaux does not teach or suggest the feature of introducing a *dominant negative allele* of a mismatch repair gene into the cells; Doutriaux does not anticipate the claims. Withdrawal of the rejection under 35 U.S.C. §102(a) is respectfully requested.

Respectfully submitted,

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